

Randomized, controlled trial of telcagepant for the acute treatment of migraine

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ABSTRACT

Background: The neuropeptide calcitonin gene-related peptide (CGRP) plays a key role in migraine pathophysiology. In this large phase 3 clinical trial, we sought to confirm the efficacy of telcagepant, the first orally bioavailable CGRP receptor antagonist.

Methods: Adults with migraine with or without aura (International Headache Society criteria) treated a moderate or severe attack with oral telcagepant 50 mg (n = 177), 150 mg (n = 381), 300 mg (n = 371), or placebo (n = 365) in a randomized, double-blind trial. The 5 co-primary endpoints were pain freedom, pain relief, and absence of photophobia, absence of phonophobia, and absence of nausea, all at 2 hours postdose. The key secondary endpoint was 2–24 hour sustained pain freedom. The prespecified primary efficacy analyses evaluated the 150 mg and 300 mg groups; the 50-mg group was included on an exploratory basis to further characterize the dose response but was not prespecified for analysis. Tolerability was assessed by adverse experience reports.

Results: Telcagepant 300 mg was more effective ($p \leq 0.001$) than placebo on all primary endpoints and the key secondary endpoint, as was telcagepant 150 mg ($p \leq 0.05$). Telcagepant 300 mg showed a slight numeric advantage over telcagepant 150 mg on most measures. Telcagepant 50 mg values were numerically intermediate between placebo and telcagepant 150 mg and 300 mg. The percentages of patients with adverse experiences were 32.2% for telcagepant 50 mg, 32.0% for telcagepant 150 mg, 36.2% for telcagepant 300 mg, and 32.2% for placebo.

Conclusions: This study confirmed previous findings that telcagepant 300 mg was effective at relieving pain and other migraine symptoms at 2 hours and providing sustained pain freedom up to 24 hours. In this study, telcagepant 150 mg was also effective. Telcagepant was generally well tolerated. *Neurology*® 2009;73:970–977

GLOSSARY

CGRP = calcitonin gene-related peptide.

Migraine is a common neurologic disorder characterized by episodic, often disabling headache, sensory, autonomic, and cognitive symptoms. The introduction in the 1990s of serotonin (5-HT)_{1B/1D} receptor agonists, the triptans, revolutionized acute therapy for migraine attacks. Triptans are effective in the majority of patients with migraine¹ and generally well-tolerated though not in all patients. Because of their potential vasoconstrictive 5-HT_{1B}-mediated effects, triptans are contraindicated in patients with coronary artery disease, cerebrovascular disease, or significant risk factors for either.² There is a need for well-tolerated migraine-specific medications that are applicable to all patient populations.

Calcitonin gene-related peptide (CGRP) is a neuropeptide with receptors found on meningeal blood vessels, trigeminal ganglion and afferents, the periaqueductal gray and other brainstem nuclei, the amygdala, and the hypothalamus.³ Elevated CGRP levels have been observed in jugular venous blood during some studies of spontaneous and nitroglycerine-provoked mi-

Supplemental data at
www.neurology.org

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graine attacks,⁴⁻⁶ but not all,⁷ and IV administration of CGRP can provoke migraine-like attacks in migraineurs.⁸

CGRP receptor antagonists are not direct vasoconstrictors,⁹⁻¹¹ and may thereby confer an advantage over triptans in the acute treatment of migraine. Proof-of-concept for the efficacy and tolerability of olcegepant, an IV CGRP receptor antagonist, in acute migraine has been reported.¹² Telcagepant (MK-0974), an oral CGRP receptor antagonist, was effective and well-tolerated for the acute treatment of migraine attacks in a phase 2b adaptive design trial¹³ and a phase 3 placebo- and active-controlled trial.¹⁴ The current study is a placebo-controlled phase 3 trial performed to confirm the efficacy and tolerability of telcagepant in the acute treatment of migraine.

METHODS Patients. Patients were eligible for the study if they were ≥ 18 years of age, had a history of migraine with or without aura for at least 1 year (International Headache Society criteria)¹⁵ and had experienced 1 to 8 moderate or severe migraine attacks per month in the 2 months prior to the screening visit, and were in good general health. Patients with a history or clinical evidence of cardiovascular disease or uncontrolled hypertension were excluded. Patients taking migraine preventative medications were allowed to enter the study provided that their prescribed daily dose had not changed during the 3 months prior to screening. Due to potential interactions with telcagepant, patients taking strong CYP3A4 inhibitors or inducers within 1 month of the screening visit were ineligible, and these medications were not permitted during the study.

Standard protocol approvals, registrations, and patient consents. The study was approved by the ethical review committee for each site and each patient provided written informed consent. The trial was registered at ClinicalTrials.gov (NCT00432237).

Study design. In this randomized, double-blind, placebo-controlled, parallel-group, outpatient study, patients treated a single migraine attack. The study (Merck Protocol 016) was conducted at 83 sites in the United States, Europe, and Latin America from March 2007 through November 2007. Patients were randomized to telcagepant 50 mg, telcagepant 150 mg, telcagepant 300 mg, or placebo in a 1:2:2:2 ratio. Patients were instructed to administer study medication when they experienced a migraine attack with moderate or severe headache. Patients had the option of taking a blinded optional second dose if they still had moderate or severe headache 2 hours after dosing or if they experienced headache recurrence within 48 hours post-initial dose. Patients randomized to telcagepant 50 mg or placebo as their initial treatment were allocated to receive the same treatment for their optional second dose, while those initially randomized to telcagepant 150 mg or 300 mg were allocated to receive either a repeat of their initial treatment or placebo in an equal ratio. The efficacy of the optional second dose is not discussed since the sample sizes were relatively small. A prespecified meta-analysis across all of the telcagepant phase 3 studies is planned.

Telcagepant and matching placebo were supplied in liquid-filled soft elastic capsules (1 capsule for each dose with matching placebo). Since the telcagepant 300-mg capsule had a different appearance from the 50-mg and 150-mg capsules, each study treatment was packaged using a double-dummy design (e.g., patients assigned to telcagepant 150 mg also received placebo matching telcagepant 300 mg). The formulation of telcagepant used in this study had a t_{max} of approximately 1–2 hours and a $t_{1/2}$ of approximately 5–8 hours. It is anticipated that the final clinical formulation will be a tablet, with similar pharmacokinetic properties to the capsule formulation.

Patients were allocated using a computer-generated randomized allocation schedule prepared by a blinded statistician at Merck, using a block size of 7. Numbered containers were used to implement allocation. Personnel at each study site used a central interactive voice response system to determine which container should be given to which patient. All study personnel, including investigators, study site personnel, patients, and Merck staff, remained blinded to treatment allocation throughout the study. Unblinding took place after data collection was complete.

Procedure. Study eligibility was assessed at a screening visit where physical examinations, vital signs, laboratory screens, and ECGs were performed. Eligible patients were randomized and provided with study medication. Patients were instructed to take study drug when they experienced a moderate or severe migraine headache. If the patient continued to have a moderate or severe headache 2 hours after dosing, or experienced headache recurrence from 2 to 48 hours after dosing, they could elect to take a blinded optional second dose of study treatment (see above), to take their own rescue medication (e.g., nonsteroidal anti-inflammatory drugs, triptans, opioids, antiemetics), or to take no further treatment.

During the 48 hours following the initial dose of study medication, patients recorded subjective assessments and use of additional medications in a paper diary, as detailed below. Patients also recorded information about any adverse experiences that occurred up to the time they returned to the clinic. Patients were instructed to return to the study site for follow-up within approximately 7 days after treatment with study medication. At this visit, the study site staff reviewed the diary, assessed medication compliance, and conducted safety assessments.

Assessments. Headache severity was assessed using a 4-grade scale (no pain, mild pain, moderate pain, severe pain) at baseline (0 hour = time of taking study medication) and at 0.5, 1, 1.5, 2, 2.5, and 24 hours postdose. The presence or absence of phonophobia, photophobia, nausea, vomiting, and ratings of functional disability (4-grade scale: normal, mildly impaired, severely impaired, requires bedrest) were recorded at the same time points as the headache severity ratings. For those patients who reported pain relief (reduction of pain to mild or none) or pain freedom (no pain) at 2 hours postdose, the presence or absence of headache worsening (recurrence) within 2–24 hours and 24–48 hours was recorded. Use of rescue medication (including the optional second dose) within 48 hours after the initial dose of study medication was also recorded. Patients also completed the Migraine-Specific Quality-of-Life Questionnaire¹⁶ 24 hours after the initial dose of study medication.

Tolerability and safety were assessed via spontaneous adverse experience reports and routine prestudy and poststudy physical and laboratory examinations, ECGs, and vital signs.

Statistical analysis. The five co-primary hypotheses were that at least one of the 150-mg or 300-mg telcagepant doses is supe-

rior to placebo, as measured by the percentage of patients at 2 hours reporting: 1) pain freedom; 2) pain relief; 3) absence of photophobia; 4) absence of phonophobia; and 5) absence of nausea. Based on a sample size of 450 patients randomized per treatment group for telcagepant 150 mg, 300 mg, and placebo (assumed to yield 382 evaluable patients per treatment group) and using a 1-sided significance level of 0.025, the study had greater than 90% power to simultaneously demonstrate significance on the five co-primary endpoints. The hypotheses, and hence the power calculation, did not apply to the telcagepant 50-mg dose, which was included in the study to further explore efficacy at the lower end of the dose range and thus had a smaller planned sample size of 225 randomized patients.

Secondary endpoints were as follows: 1) 2- to 24-hour sustained pain freedom (pain free from 2 to 24 hours without the use of rescue medication, including the optional second dose); 2) total migraine freedom at 2 hours (no pain, photophobia, phonophobia, nausea, or vomiting); and 3) 2- to 24-hour total migraine freedom (2- to 24-hour sustained pain freedom with no photophobia, phonophobia, nausea, or vomiting from 2 to 24 hours). The key secondary endpoint was 2- to 24-hour sustained pain freedom.

The full analysis set was the primary population for assessing efficacy. For each co-primary endpoint, the full analysis set included all treated patients who had a baseline headache severity score and at least one postdose measurement occurring at or prior to 2 hours postdose. Non-baseline missing data were imputed using a last observation carried forward approach. Patients were counted in the treatment group to which they were randomized. Patients who took the initial telcagepant dose (50 mg, 150 mg, or 300 mg) were considered to be a part of the same treatment group (50 mg, 150 mg, or 300 mg) regardless of the optional second dose.

The response rates and odds ratios in the telcagepant 150 mg, 300 mg, and placebo groups were estimated using a logistic model with categorical terms for treatment, geographic region (United States, non-United States), and baseline headache severity (moderate or severe), with age included as a continuous covariate. To control for multiplicity, a step down closed testing procedure¹⁷ was applied to the five co-primary hypotheses and the key secondary hypothesis, each at a significance level of 0.05. The hierarchy of hypothesis testing, numbered in order of testing, is shown in table e-1 on the *Neurology*[®] Web site at www.neurology.org.

Additional prespecified exploratory analyses were performed involving the above measures at additional time points (e.g., pain relief at time points other than 2 hours, 2- to 48-hour sustained pain freedom) or different measures (e.g., functional disability, migraine quality of life). Findings of interest from these analyses are also presented. Since telcagepant 50 mg was primarily included in the study to further explore efficacy at the lower end of the dose range, no formal statistical comparisons between telcagepant 50 mg and placebo were performed.

An exploratory step-down trend test for dose was conducted for the 2-hour pain freedom and pain relief measures using a logistic regression model with categorical terms for geographic region and baseline headache severity, and with dose (0 mg/placebo, 50 mg, 150 mg, 300 mg) and age as continuous variables. The trend test was based on the estimate of the slope coefficient for the dose level variable. All 4 treatment groups were included in the trend test at the first step to evaluate whether there was substantial evidence of a dose-related trend in efficacy across all doses included in this study. To further evalu-

ate the contribution of individual doses to the trend analysis result, a sequential procedure that evaluated progressively smaller subsets of the treatment groups was employed. Specifically, if the test was significant at the 0.05 level, then the test was repeated excluding the top dose and so on in a stepwise fashion until there was only one dose remaining or until nonsignificance was observed.

All patients who were randomized and took study treatment were included in the safety assessment. All adverse experiences reported up to 14 days following study treatment were included. The percentages of patients with any adverse experiences, any serious adverse experiences, and the most commonly occurring adverse experiences were calculated for each treatment group. In order to fully characterize the tolerability profile of telcagepant, a separate analysis was also performed using adverse experiences within the first 48 hours after dosing, on the assumption that those occurring soonest after dosing were most likely to be attributable to study drug.

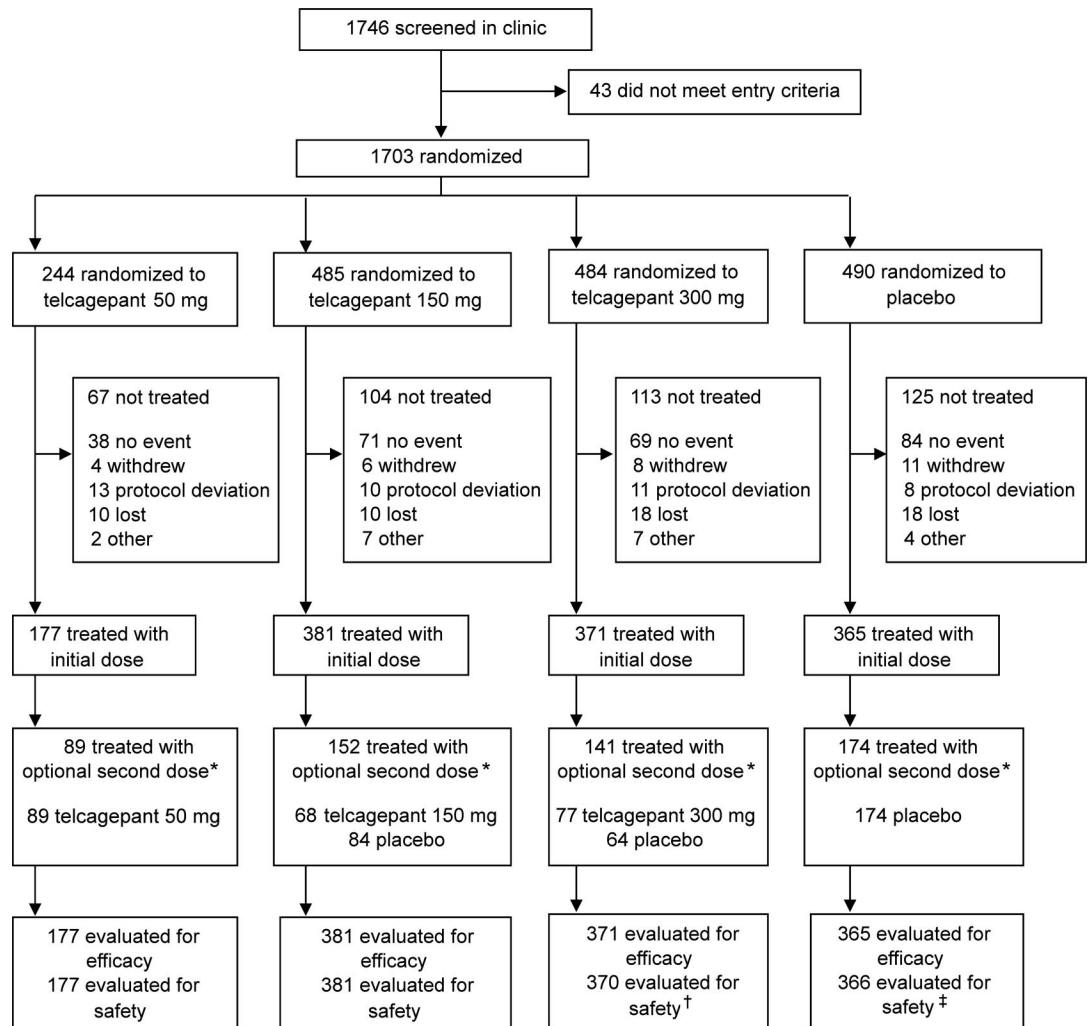
RESULTS Patient accounting and demographics.

The trial profile is shown in the figure. A total of 1,294 patients were treated. Of these, 562 were from European sites, 169 were from Central and South American sites, and 563 were from sites in the United States. Characteristics of the patients taking treatment and baseline characteristics of their treated migraine attacks are summarized in table 1. The treatment groups had generally similar demographic profiles and baseline attack characteristics.

Efficacy. The percentages of responders in each treatment group are shown in table 2 for each of the primary and secondary endpoints. Based on the closed testing procedure and the logistic regression model, both telcagepant 300 mg and 150 mg were superior to placebo on all five co-primary 2-hour endpoints as well as on the key secondary endpoint of 2- to 24-hour sustained pain freedom (table e-1). Although formal statistical testing was not performed for telcagepant 50 mg vs placebo, visual inspection of the observed response proportions suggests that the efficacy of the 50-mg dose was intermediate between placebo and the 2 higher telcagepant doses for all primary and secondary endpoints. A similar pattern of results was observed for the exploratory measures, including 2- to 24-hour sustained pain relief, 2- to 48-hour sustained pain relief and pain freedom, functional disability, and quality of life assessments (table 3).

Telcagepant 300 mg and 150 mg appeared to have similar efficacy, although telcagepant 300 mg tended to be numerically slightly more effective on most measures. Both telcagepant 300 mg and 150 mg appeared numerically more effective than telcagepant 50 mg. The results of the dose-response trend analysis for pain freedom at 2 hours indicated a dose-response relationship over the 0 to 300 mg dose

Figure Trial profile



*Patients had the option of taking a blinded second dose of study drug if the headache was still moderate or severe at 2 hours or for headache recurrence within 48 hours. †One fewer than the number initially treated because a patient randomized to telcagepant 300 mg took her sister's medication instead (the sister was also in the study and was assigned to placebo). ‡One more than the number initially treated because of the patient randomized to telcagepant 300 mg who took placebo.

range ($p < 0.001$) and the 0 to 150 mg dose range ($p < 0.01$), but not for the 0 to 50 mg dose range ($p = 0.06$). For pain relief at 2 hours, the dose-response trend analysis indicated a dose-response relationship over the 0 to 300 mg dose range ($p < 0.001$), the 0 to 150 mg dose range ($p < 0.01$), and the 0 to 50 mg dose range ($p = 0.01$).

Tolerability and safety. Telcagepant was generally well-tolerated in the acute treatment of migraine. Adverse experiences occurring up to 48 hours after dosing are summarized in table 4. The percentage of patients with adverse experiences was slightly higher for telcagepant 300 mg compared with placebo, although statistical analyses were not performed. Telcagepant 150 mg and 50 mg had adverse experience rates that were similar to placebo. Among the most common specific adverse experiences (incidence

$\geq 2\%$ in at least one of the treatment groups), the following showed a numerical increase compared to placebo for at least one dose of telcagepant: fatigue, dizziness, nausea, upper abdominal pain, somnolence, and vomiting. For telcagepant 300 mg, the most common specific adverse experiences showing a numerical increase compared to placebo were fatigue, dizziness, and upper abdominal pain. The majority of adverse experiences occurred during the first 48 hours after dosing and the tolerability profile in the analysis looking at adverse experiences occurring up to 14 days after dosing (table e-2) was very similar to that described above for adverse experiences occurring within 48 hours. No patients died during the study. There were 2 serious adverse experiences: 1 in a patient who received placebo (closed head injury) and 1 in a patient who received telcagepant 150 mg

Table 1 Characteristics of patients and the treated migraine attack at baseline

	Placebo (n = 365)	Telcagepant 50 mg (n = 177)	Telcagepant 150 mg (n = 381)	Telcagepant 300 mg (n = 371)
Patient characteristics				
Mean (SD) age, y	41.9 (11.9)	41.4 (11.3)	41.6 (11.0)	41.8 (11.6)
Women	318 (87.1)	156 (88.1)	329 (86.4)	320 (86.3)
White	303 (83.0)	148 (83.6)	320 (84.0)	302 (81.4)
Using prophylaxis	67 (18.4)	37 (20.9)	64 (16.8)	62 (16.7)
Usual acute migraine treatment				
None	8 (2.2)	4 (2.3)	3 (0.8)	3 (0.8)
NSAID	96 (26.3)	43 (24.3)	104 (27.3)	107 (28.8)
Triptan	166 (45.5)	78 (44.1)	166 (43.6)	151 (40.7)
NSAID and triptan	56 (15.3)	28 (15.8)	67 (17.6)	57 (15.4)
Other	39 (10.7)	24 (13.6)	40 (10.5)	53 (14.3)
Baseline characteristics of treated attack				
Aura	82 (22.5)	43 (24.3)	95 (24.9)	84 (22.6)
Moderate headache	235 (64.4)	108 (61.0)	254 (66.7)	237 (63.9)
Severe headache	130 (35.6)	69 (39.0)	127 (33.3)	133 (35.8)
Phonophobia	261 (71.9)	—	293 (76.9)	274 (74.5)
Photophobia	299 (82.1)	—	315 (82.9)	301 (81.8)
Nausea	221 (60.7)	—	209 (55.4)	226 (61.4)
Vomiting	23 (6.4)	—	19 (5.0)	30 (8.2)
Baseline function for treated attack				
Normal	14 (3.8)	—	16 (4.2)	16 (4.3)
Mildly impaired	193 (52.9)	—	192 (50.4)	182 (49.2)
Severely impaired	116 (31.8)	—	133 (34.9)	124 (33.5)
Requiring bedrest	42 (11.5)	—	40 (10.5)	47 (12.7)

Values are number (%) of patients, except for age, where the mean (SD) is given. N = number of treated patients; sample sizes differed slightly from this for some characteristics due to missing data. Likewise, some percentages do not add up to 100% (e.g., the different categories of baseline function) due to missing data. Data on baseline associated symptoms and function were not calculated for telcagepant 50 mg.

NSAID = nonsteroidal antiinflammatory drug.

(hypertension). The serious adverse experience of hypertension occurred at the posttreatment clinic visit 4 days after administration of telcagepant 150 mg. The patient experienced a migraine attack and blood pressure elevation (170/106). The patient took eletriptan and experienced pain resolution after 2 hours but blood pressure remained elevated (180/120) and she was admitted for observation. The patient had a previous medical history of hypertension which was diagnosed 3 years before but was not active at the time of study enrollment. Neither serious adverse experience was considered to be related to study drug by the investigator (determination made while blinded to treatment).

Laboratory abnormalities during the study were uncommon and no clinically relevant differences

were seen between treatment groups. Other assessments, including the percentage of patients who exceeded predefined levels of change on laboratory parameters, vital sign measurements, ECG measurements, and physical examinations, indicated no clinically meaningful differences between treatment groups.

DISCUSSION This large phase 3 study supports the hypothesis that CGRP plays an important role in migraine pathogenesis and that oral CGRP receptor antagonists such as telcagepant are effective in treating migraine symptoms of headache, photophobia, phonophobia, and nausea, with tolerability similar to placebo. In patients who treated a single migraine attack, doses of 150 or 300 mg of telcagepant were significantly more effective than placebo on all primary and secondary endpoints. Telcagepant 300 mg and 150 mg appeared to have similar efficacy, although telcagepant 300 mg tended to be slightly more effective on most measures. The 50 mg dose was not statistically tested but demonstrated numerical effects that were intermediate between placebo and telcagepant 150 mg and 300 mg.

The results of the present study are in general agreement with the previous phase 3 trial comparing 150 and 300 mg telcagepant with placebo or 5 mg zolmitriptan.¹⁴ Efficacy rates for 2-hour pain freedom following telcagepant 300 mg were comparable in the 2 studies (23.8% in the current study and 26.9% in the previous study). The efficacy of 150 mg appeared more similar to 300 mg in the present study than in the previous study, but no statistical testing between these 2 telcagepant doses was performed in either study.

In agreement with the phase 2 study¹³ and the previous phase 3 study,¹⁴ telcagepant was well-tolerated with an adverse experience profile similar to that of placebo. Specific adverse experiences which were slightly more common for telcagepant 300 mg than placebo in this study were fatigue, dizziness, and upper abdominal pain. No clinically relevant changes in laboratory measures, including transaminase levels, were seen although these were assessed up to 7 days or more after dosing.

The strength of the present study is the large sample size of patients who typify the migraine study population with baseline characteristics well-balanced across treatment groups. Another strength is the wide range of primary and secondary outcome parameters which were prespecified in the analysis and selected exploratory endpoints which included functional disability and quality of life outcomes.

Table 2 Summary of efficacy for primary and secondary endpoints: Percentage of patients (95% CI)

Endpoint	Placebo (n = 365)	Telcagepant 50 mg (n = 177)*	Telcagepant 150 mg (n = 381)	Telcagepant 300 mg (n = 371)
Primary				
Pain freedom 2 h	10.7 (7.7, 14.3)	16.5 (11.3, 22.8)	23.2 (19.0, 27.7)*	23.8 (19.6, 28.5)*
Pain relief 2 h	32.9 (28.1, 38.0)	44.3 (36.8, 52.0)	53.9 (48.8, 59.0)*	55.6 (50.3, 60.7)*
No phonophobia 2 h	41.6 (36.5, 46.9)	48.3 (40.7, 55.9)	50.5 (45.4, 55.7)*	55.8 (50.6, 61.0)*
No photophobia 2 h	32.6 (27.8, 37.7)	40.9 (33.6, 48.6)	46.3 (41.2, 51.5)*	48.5 (43.3, 53.7)*
No nausea 2 h	53.7 (48.4, 58.9)	64.2 (56.6, 71.3)	68.6 (63.7, 73.2)*	69.9 (65.0, 74.6)*
Secondary				
2- to 24-h sustained pain freedom	7.2 (4.7, 10.3)	14.1 (9.4, 20.1)	16.4 (12.8, 20.5)*	17.3 (13.5, 21.5)*
Total migraine freedom 2 h	9.9 (7.0, 13.4)	13.6 (8.9, 19.6)	20.5 (16.6, 24.9)*	21.1 (17.1, 25.7)*
2- to 24-h total migraine freedom	6.3 (4.1, 9.4)	11.3 (7.0, 16.9)	14.6 (11.2, 18.5)*	14.8 (11.3, 18.9)*

The observed (not model-based) percentages and corresponding confidence intervals are presented. N = number of treated patients; the actual sample sizes in the full analysis set population differed slightly from N for some endpoints due to missing data. p Values were computed using a logistic model adjusting for baseline severity, geographic region, and age.

*No comparisons between telcagepant 50 mg and placebo were performed.

†p ≤ 0.001, ‡p ≤ 0.050. For the telcagepant-placebo pairwise comparison.

Functional outcomes clearly showed decreased impairment and improved quality of life scores with telcagepant over placebo.

Although telcagepant is not a direct vasoconstrictor and in principle is therefore safe for use in patients with known vascular disease, such patients

Table 3 Summary of efficacy for selected exploratory endpoints

Endpoint	Placebo (n = 365)	Telcagepant 50 mg (n = 177)*	Telcagepant 150 mg (n = 381)	Telcagepant 300 mg (n = 371)
Headache, % of patients (95% CI)†				
2- to 48-h sustained pain freedom	5.8 (3.6, 8.8)	11.4 (7.1, 17.1)	13.5 (10.2, 17.4)*	15.7 (12.1, 19.9)*
2- to 24-h sustained pain relief	19.3 (15.4, 23.8)	25.6 (19.3, 32.7)	33.7 (28.9, 38.7)*	36.6 (31.7, 41.8)*
2- to 48-h sustained pain relief	15.7 (12.1, 19.9)	20.1 (14.4, 26.8)	28.5 (23.9, 33.4)*	32.3 (27.5, 37.4)*
Functional disability 2 h, % of patients‡				
Normal	15.9	—	29.4†	30.8†
Mildly impaired	34.8	—	40.2	39.7
Severely impaired	24.4	—	17.6	15.7
Requiring bedrest	24.9	—	12.6	13.5
Migraine quality-of-life 24 h, mean (SE) score¶				
Work functioning	11.9 (0.3)	—	12.9 (0.3)¶	12.9 (0.3)¶
Social functioning	11.7 (0.3)	—	12.7 (0.3)¶	13.2 (0.3)*
Energy/vitality	11.0 (0.3)	—	12.1 (0.3)¶	12.5 (0.3)*
Migraine symptoms	12.2 (0.3)	—	13.5 (0.3)*	14.1 (0.3)*
Feelings/concerns	11.0 (0.3)	—	12.3 (0.3)*	12.8 (0.3)*

N = number of treated patients; the actual sample sizes in the full analysis set population differed slightly from N for some endpoints due to missing data. The observed (not model-based) percentages and corresponding confidence intervals are presented.

*No comparisons between telcagepant 50 mg and placebo were performed. In addition, no descriptive statistics were calculated for the functional disability or migraine quality-of-life assessments.

†p Values were computed using a logistic model adjusting for baseline severity, geographic region, and age.

‡p ≤ 0.001, ¶p ≤ 0.010. For the telcagepant-placebo pairwise comparison.

§Nominal p values (p < 0.001) were obtained using both an analysis in which functional disability was dichotomized to normal/not normal and a cumulative logistic model analysis. Both models adjusted for baseline severity, geographic region, and age.

¶The range of scores for each domain is 3 to 21, with a higher score indicating better quality of life. p Values were computed using an analysis of covariance model adjusted for geographic region, baseline severity, and age.

Table 4 Summary of n (%) of patients reporting any adverse experience, and specific clinical adverse experiences with an incidence $\geq 2\%$ in any treatment group, within 48 hours postdose

Adverse experience	Placebo (n = 366)	Telcagepant 50 mg (n = 177)	Telcagepant 150 mg (n = 381)	Telcagepant 300 mg (n = 370)
Any	113 (30.9)	57 (32.2)	117 (30.7)	128 (34.6)
Specific adverse experiences				
Fatigue	14 (3.8)	9 (5.1)	14 (3.7)	24 (6.5)
Dizziness	12 (3.3)	13 (7.3)	9 (2.4)	20 (5.4)
Dry mouth	19 (5.2)	9 (5.1)	17 (4.5)	19 (5.1)
Nausea	20 (5.5)	14 (7.9)	13 (3.4)	17 (4.6)
Abdominal pain, upper	6 (1.6)	1 (0.6)	4 (1.0)	12 (3.2)
Somnolence	11 (3.0)	7 (4.0)	14 (3.7)	10 (2.7)
Paraesthesia	9 (2.5)	3 (1.7)	5 (1.3)	8 (2.2)
Vomiting	10 (2.7)	5 (2.8)	3 (0.8)	6 (1.6)
Vertigo	9 (2.5)	3 (1.7)	2 (0.5)	5 (1.4)
Headache	8 (2.2)	0 (0.0)	3 (0.8)	2 (0.5)

were excluded from the current trial. The exclusion was made under guidance from the Food and Drug Administration pending the availability of phase 1 safety data in patients with cardiovascular disease. A dedicated phase 3 outpatient study in patients with both migraine and stable cardiovascular disease is ongoing to help guide the appropriate use of telcagepant in this population (NCT00662818). Additional studies to investigate the long-term efficacy, tolerability, and consistency of response for telcagepant are in progress (NCT00443209 and NCT00483704).

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by James Kost, Xiaoyin Fan, and Christopher Assaid from Merck Research Laboratories.

DISCLOSURE

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APPENDIX

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